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Centrality of prefrontal and motor preparation cortices to Tourette Syndrome revealed by meta-analysis of task-based neuroimaging studies

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Abstract

Tourette Syndrome (TS) is a neurodevelopmental condition characterized by chronic multiple tics, which are experienced as compulsive and 'unwilled'. Patients with TS can differ markedly in the frequency, severity, and bodily distribution of tics. Moreover, there are high comorbidity rates with attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety disorders, and depression. This complex clinical profile may account for apparent variability of findings across neuroimaging studies that connect neural function to cognitive and motor behavior in TS.

Here we crystalized information from neuroimaging regarding the functional circuitry of TS, and furthermore, tested specifically for neural determinants of tic severity, by applying activation likelihood estimation (ALE) meta-analyses of neuroimaging (activation) studies of TS. Fourteen task-based studies (13 fMRI and one H2O-PET) met rigorous inclusion criteria. These studies, encompassing 25 experiments and 651 participants, tested for differences between TS participants and healthy controls across cognitive, motor, perceptual and somatosensory domains.

Relative to controls, TS participants showed distributed differences in the activation of prefrontal (inferior, middle, and superior frontal gyri), anterior cingulate, and motor preparation cortices (lateral premotor cortex and supplementary motor area; SMA). Differences also extended into sensory (somatosensory cortex and the lingual gyrus; V4); and temporo-parietal association cortices (posterior superior temporal sulcus, supramarginal gyrus, and retrosplenial cortex).

Within TS participants, tic severity (reported using the Yale Global Tic Severity Scale; YGTSS) selectively correlated with engagement of SMA, precentral gyrus, and middle frontal gyrus across tasks.

The dispersed involvement of multiple cortical regions with differences in functional reactivity may account for heterogeneity in the symptomatic expression of TS and its comorbidities. More specifically for tics and tic severity, the findings reinforce previously proposed contributions of premotor and lateral prefrontal cortices to tic expression.

Keywords: activation likelihood estimation (ALE), meta-analysis, fMRI, supplementary motor area (SMA), tic disorder, Tourette syndrome

1. Introduction

Tourette syndrome (TS) is a neurodevelopmental condition characterized by the chronic expression of multiple motor and phonic tics. Tics are rapid, recurrent actions or vocalisations that may range in complexity from simple brief acts such as eye blinks or coughs, to elaborate action sequences. Tics are highly variable in their presentation among individuals, with substantial differences in the frequency, complexity, and bodily location of tics.

Tics show a number of distinctive features. They often exhibit a classical ‘waxing and waning’ in severity and presentation over time (Burd et al., 2001; Leckman et al., 2006; Robertson, 2000), and are typically exacerbated by anxiety, stress, and fatigue (Conelea and Woods, 2008). Although tics are commonly assumed to be compulsive and ‘unwilled’, they can be more accurately described as ‘unvoluntary’, in that an involuntary urge to move can be relieved by a volitional decision to release the tic (Cavanna and Nani, 2013; Jankovic, 1997). These ‘premonitory’ urges often (though not always) precede tics and occur in up to 90% of adolescents with TS (Bloch and Leckman, 2009).

Such premonitory experiences often take the form of uncomfortable sensory symptoms, and are not only subjectively perceived by patients as a key precursor event in tic expression, but are furthermore associated with greater tic severity, greater functional impairment, and poorer quality of life (Crossley and Cavanna, 2013; Rozenman et al., 2015).

TS is a neurodevelopmental disorder, with onset of tics in childhood or adolescence. However, the lifespan trajectory is highly variable: more than 50% of people with TS may experience a substantial decline in tic severity by early adulthood; some may undergo complete remission; and some continue to experience tics into adulthood, sometimes accompanied by an increase in tic severity (Cohen et al., 2013; Hassan and Cavanna, 2012).

The heterogeneous presentation of TS is reflected not only in the individual expression of tics, but also in the expression of common comorbidities (Robertson, 2000). Perhaps only 10% of TS patients have ‘pure’ TS (i.e. tics only) (Cavanna et al., 2009). The majority of TS individuals present with comorbidities, i.e. as ‘TS+’. The two most frequent comorbid conditions are obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD), each showing comorbidity rates of 30%-50% (Cohen et al., 2013). Arguably tic disorders, OCD, and ADHD share core behavioural and psychological features. Correspondingly, within the brain, there is overlap in putative neuroanatomical substrates, implicating fronto-striatal network dysfunction (Worbe et al.,

2013). However, distinct phenotypes are likely to arise from particular developmental profiles in (epi-) genetic architecture (Davis et al., 2013) that determine divergent clinical expression (Cohen et al., 2013). Affective symptomatology, including depression and anxiety, is also more common among patients with TS than in the general population (Cavanna and Nani, 2013; Yang et al., 2017).

TS is linked to aberrant functioning of several neurotransmitters, including dopaminergic, glutamatergic and GABAergic systems (Buse et al., 2013; Ganos et al., 2013; Jackson et al., 2015; Kanaan et al., 2017; Puts et al., 2015). Prescribed pharmacotherapies most commonly target dopaminergic transmission, but are not effective in all individuals at reducing tics (Buse et al., 2013), further highlighting the heterogeneity of the condition.

Theoretical and empirical knowledge suggests broadly that TS is underpinned by dysfunction within cortico-striato-thalamo-cortical (CSTC) motor networks (Alexander et al., 1986; Ganos et al., 2013; Jackson et al., 2015; Worbe et al., 2013). These circuits underpin habitual motor behavior including the transition of goal-directed action selection to compulsive action (Everitt and Robbins, 2016; Graybiel, 2008). Furthermore, disorders with clear CSTC dysfunction incorporating overlapping symptoms with TS such as compulsivity in OCD (Vaghi et al., 2017), or opponent symptoms such as bradykinesia in Parkinson's disease (Alexander et al., 1986), highlight the relevance of basal ganglia interactions for tics. Additional cortical and subcortical systems are also implicated in the general expression of TS, including regions supporting motor planning and preparation, executive function, somatosensation and perception (Cavanna et al., 2017; Ganos et al., 2013; Worbe et al., 2015).

Although there are multiple reported functional differences of neural activity in TS, many are not explicitly linked to expression of particular symptoms. For example, in a prepulse inhibition (PPI) paradigm, children and adults with TS show widespread alterations in activity across distributed anatomical areas compared to controls, suggesting non-specific changes in somatosensory gating (Buse et al., 2016a; Zebardast et al., 2013). In studies examining motor inhibition, of particular relevance to tic suppression, TS patients show functional differences in motor control and motor execution regions (Ganos et al., 2014; Thomalla et al., 2014), yet it is difficult to determine if these reflect disruption or enhancement of inhibitory control, and may be obfuscated by participants with heterogeneous developmental courses and comorbid ADHD (Jackson et al., 2015). Finally, abnormal neural activation is reported for TS individuals during simple motor tasks (Roessner et al., 2013; Zapparolet al., 2016), during mentalization (theory of mind) (Eddy et al., 2017; Eddy et al., 2016),

and during emotional face perception (Neuner et al., 2010). However, abnormalities are not consistent: for example, in one study, no differences were observed between adolescents with TS and controls during tests spanning cognitive and motor domains (Debes et al., 2011).

Taken together, these findings indicate that functional neuroanatomical differences associated with TS are perhaps subtle, yet extend beyond motor circuitry into neural substrates supporting many domains of cognitive function. Specific functional differences may relate to the core symptoms of tics and premonitory sensations (Cavanna et al., 2017), or reflect facets of common comorbidities (Debes et al., 2017), distinct developmental trajectories (Jackson et al., 2015), or even dysfunction impacting multiple neural systems, such as a tendency towards cortical hyperexcitability (Draper et al., 2015). Historically, the assimilation of disparate results from functional neuroimaging studies on TS populations is challenging on account of substantial participant heterogeneity in tic experience, lifespan expression, comorbidity rate, and medication usage (Ganos et al., 2013). Furthermore, the different functional systems in which there are potential differences between TS and control populations are reflected in the different cognitive tasks applied by functional imaging studies, and in the neuroanatomical distribution of identified functional changes that extend beyond canonical CSTC networks (Debes et al., 2017; Ganos et al., 2013).

In the current study, we use a meta-analytic approach to synthesize the existing neuroimaging literature of task-based fMRI studies in TS populations. We conducted a series of activation likelihood estimation (ALE) meta-analyses (Eickhoff et al., 2009; Turkeltaub et al., 2002) to improve statistical power compared to a single study, and capitalize upon evidence from studies with different sample characteristics and experimental designs, to elucidate common neurobiological substrates related to TS.

We first tested for group differences between TS and control participants in neural activation, across cognitive domains. Next, given the mixed comorbidity samples employed in the literature, we determined which patterns of functional neural reactivity specifically relate to tics (as core TS symptoms), by examining association between neural activations and tic severity score, across the various experimental tasks employed. This combined approach provides an overview of the existing task-based neuroimaging data on TS, and further pinpoints specific functional neuroanatomy alterations that are central to TS, beyond comorbidities.

2. Methods

2.1. Literature Search

A literature search on Pubmed (www.ncbi.nlm.nih.gov/pubmed) was conducted using the following search terms: “Tourette” OR “Tourette Syndrome” OR “Tourette’s Syndrome” AND “fMRI” OR “functional magnetic resonance imaging” OR “PET” OR “positron emission tomography”. Only studies that met the following inclusion criteria were considered for analysis:

1. Original data is presented (thus, review papers were excluded),
2. Tourette Syndrome sample was examined (excluding studies on patients with secondary tics after e.g. traumatic brain injury, stroke, encephalitis, and patients with Tourette-like symptoms called Tourettisms),
3. Study included a control group and reports TS vs Control contrast(s)
4. Methods include task-related fMRI or H2O-PET (excluding e.g. diffusion tensor imaging (DTI), voxel-based morphometry (VBM), behavioral only, and non-task-related fMRI studies such as resting-state fMRI),
5. Participants were not subjected to treatment therapies as part of the experimental manipulation (e.g. deep brain stimulation (DBS) or drug infusion; exception: behavioral therapy),
6. Whole-brain analysis was conducted (excluding studies reporting only region of interest (ROI) analyses),
7. Peak activation coordinates are reported,
8. Study was conducted with human participants,
9. Article was originally published in English.

Figure 1 provides a detailed illustration of the literature selection process.

2.2. Study Selection

As of January 2017, fourteen publications met inclusion criteria for the first ALE analysis examining differences between TS and control participants (see **Supplementary Table 1** for references). If otherwise suitable studies did not report activation coordinates, we contacted the authors by e-mail. However, all enquiries remained unsuccessful. Likewise, we contacted the authors

of three papers who did not report the age range of the participants (Debes et al., 2011; Mazzone et al., 2010; Roessner et al., 2012) to request these. This information was available for one study (Roessner et al., 2012). The age of the participants from the other two studies (Debes et al., 2011; Mazzone et al., 2010) is therefore described with the mean and standard deviation, as reported within the original publications. The following information was recorded for each study: first author and year of publication, neuroimaging method (fMRI/H₂O-PET), task domain, brief task description and contrast(s) entered to the ALE, sample size of TS and control groups, age range of TS participants (in all studies, case and control participants were age-matched), number of TS participants with comorbid OCD and ADHD, and their medication status (**Table 1**). Notably, if two studies presented different data acquired from the same sample, both were included as separate experiments (Eddy et al., 2017; Eddy et al., 2016).

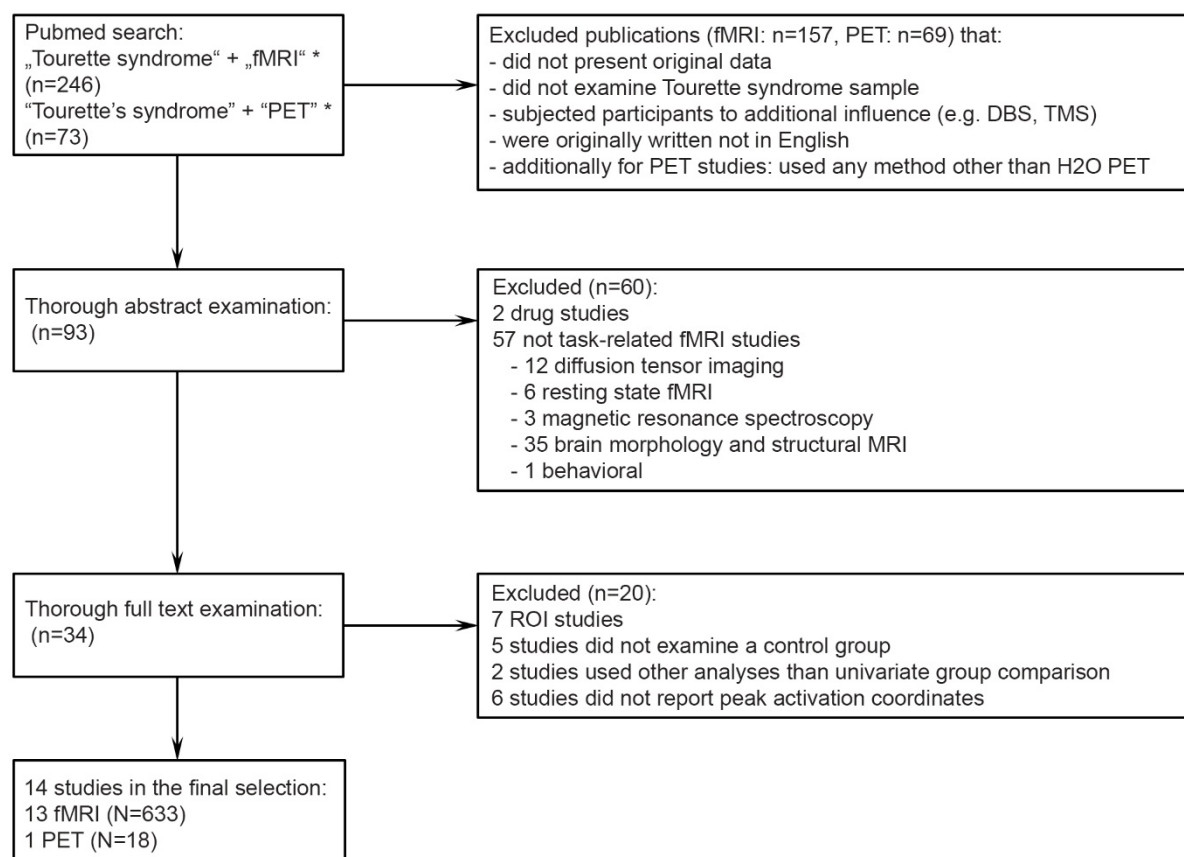


Figure 1. Flow chart describing the literature selection process. Number of publications (n) and number of individuals (N) are indicated. * We tested all combinations of search terms “Tourette”, “Tourette Syndrome”, “Tourette’s Syndrome” AND “fMRI”, “functional magnetic resonance imaging”

OR “PET”, “positron emission tomography”. Searches other than those indicated in the figure did not provide additional results.

Two studies (Buse et al., 2016b; Debes et al., 2011) found no difference between the TS and control groups and were thus entered into the meta-analysis with no coordinates. Three other studies (Mazzone et al., 2010; Zapparoli et al., 2016; Zebardast et al., 2013) conducted an ANOVA analysis, and we selected information equivalent to the TS vs control contrast from reported main effects and interactions. Interactions were only used if the direction of the effect was clearly described, and relevant to group differences. For example, in a study of prepulse inhibition in TS and control participants, a reported Task x Group interaction reflected activation differences between TS and control groups for the contrast of PPI trials compared to ‘pulse alone’ trials (Zebardast et al., 2013). In addition, some articles provided more than one analysis comparing TS and control participants. For example, in a study of finger tapping, TS and control participants were compared on finger tapping with the right hand in one analysis, and on finger tapping with the left hand in another (Roessner et al., 2013). These contrasts were included in the meta-analysis as separate experiments. Contrasts examining decreases [TS < control] and increases [TS > control] in activation for the TS group were pooled and included in one experiment as [TS vs control]. The final selection of publications provided 25 experiments, 311 foci, and a total of 651 participants.

First Author	Year	fMRI/ PET- H2O	No. TS	No. Con	Age TS (range)	OCD/ADHD	Meds	Task Nature	Task: Contrast	Group Contrast
Buse (a)	2016	fMRI	22	22	Adolescents (11-17)	-	9	Somatosensory	PPI: prepulse > pulse alone	Con > TS
Buse (b)	2016	fMRI	17	23	Adolescents (11-17)	-	5	Auditory	Harmonic expectancy violation paradigm: harmonic vs disharmonic	TS vs Con (main effect)
Debes	2011	fMRI	39	37	Adolescents (M=13.9, SD=2.1)	12/7	-	Cognitive, Motor	Stroop: correct congruent vs correct incongruent Go-No-Go: correct no-go vs correct go Finger tapping: finger tapping vs rest	TS vs Con
Eddy	2017	fMRI	23	24	Adults (17-59)	-	10	Cognitive	Mental state judgement: mental state judgement vs rest, age judgement vs rest	TS > Con Con > TS
Eddy	2016	fMRI	24	24	Adults (17-59)	-	10	Cognitive	ToM: false belief > false photo	Con > TS (across tasks) FB > FP & Con > TS
Ganos	2014	fMRI	14	15	Adults (18-46)	-	3	Cognitive	Visual stop-signal task: stop-success > go	Con > TS

Lerner	2007	PET-H2O	9	9	Adults (20-44)	7/5	-	Motor	Release of tics: tics > sleep (TS) Sleep stage 2: rest > sleep (TS), rest > sleep (Con)	TS > Con (tics) TS vs Con (sleep)
Mazzone	2010	fMRI	51	69	Adolescents (M=13.1, SD=2.6) Adults (M=35.1, SD=11.1)	40/17	21	Motor & Cognitive	Blinking & blink inhibition: inhibition vs blinking	TS vs Con (main effect) Age x Group (interaction)
Neuner	2010	fMRI	19	19	Adults (18-55)	6/3	11	Visual	Face perception: face vs rest	TS vs Con
Roessner	2013	fMRI	22	22	Adolescents (10-14)	-	-	Motor	Finger tapping: right hand vs rest, left hand vs rest	TS > Con Con > TS
Roessner	2012	fMRI	14	15	Adolescents (9-15)	-	-	Motor	Finger tapping: tapping vs rest	TS > Con Con > TS
Werner	2011	fMRI	19	18	Adults (22-52)	4/2	9	Motor	Finger tapping: right hand > baseline, left hand > baseline, both hands > baseline, both > (0.5*[Right] + 0.5*[Left])	TS > Con Con > TS
Zapparoli	2016	fMRI	24	24	Adults (19-54)	16/0	17	Motor	Execute movement: right hand > rest,	TS > Con (movement execution)

									left hand > rest Imagine movement: right hand > rest, left hand > rest	TS > Con (movement imagery)
Zebardast	2013	fMRI	17	16	Adults (21-59)	12/9	Many*	Somatosensor y	PPI: prepulse > pulse alone	Task x Group Interaction

Table 1. Studies included in the ALE meta-analysis examining differences in activations between TS participants and controls.

No. TS/Con – number of TS and control participants, respectively. OCD/ADHD – number of TS participants with comorbid OCD or ADHD. Meds – number of TS participants on medication. PPI – prepulse inhibition. ToM – Theory of Mind.

* Publication provides only the percentages of TS patients who take certain medications, which, however, are not mutually exclusive. It is thus not possible to report exactly how many patients were on medication.

2.3 ALE Meta-analysis: TS vs controls group difference

First, we examined differences in activations between TS participants and controls. The meta-analysis was performed using GingerALE 2.3.6. (<http://brainmap.org/ale>). The Activation Likelihood Estimation (ALE) algorithm treats the reported foci of included studies as spatial probability distributions centered on the given coordinates (Eickhoff et al., 2009; Turkeltaub et al., 2002). The width of the distribution depends on empirical estimates of between-subject and between-template variability, also accounting for the sample size of each experiment. Further, a ‘modelled activation’ (MA) map is computed by merging the probability distributions of all foci reported in the respective experiment. The ALE image is then produced by taking the union of all MA maps in a voxel-wise manner. The algorithm subsequently searches for above-chance convergence of activation probabilities between experiments. This allows for a random-effect analysis, as opposed to considering between-foci convergence that would produce a fixed-effects analysis, thereby permitting generalization of the results to experiments not included in the meta-analysis. Finally, the results are tested against a null distribution that assumes random spatial association between experiments. Our approach therefore followed the details of established ALE methodology (Eickhoff et al., 2012).

Stereotactic brain coordinates reported in Talairach space were converted to MNI using Talairach to MNI (SPM) conversion as implemented in GingerALE. Default settings were used with the exception of setting the ALE Method to “Turkeltaub Non-Additive”, which controls within-experiment effects by limiting probability values of neighboring foci from the same experiment. This is achieved using the maximum probability associated with a given focus (as opposed to using the union of the probabilities) for computing the MA map (Turkeltaub et al., 2012). The ALE map was thresholded at $p < 0.001$ uncorrected with a minimum cluster volume of 100 mm^3 (Boeckle et al., 2016; Jia and Yu, 2017). The ALE map was displayed using MRICron (www.mccauslandcenter.sc.edu/crnl), and anatomical labeling was guided by the Anatomy toolbox 2.2b (Eickhoff et al., 2007) for SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/ext/#Anatomy>, www.fil.ion.ucl.ac.uk/spm/software/spm12), and the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006) in FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>).

2.3.1 TS vs controls group difference: additional task-based studies employing region of interest (ROI) approaches

Four studies that otherwise met inclusion criteria employed an ROI analysis method whereby the whole-brain effect of task, for both TS and control participants, was used to define a ‘task ROI’ to which a small volume correction was applied when interrogating the group difference between TS and control participants. These four studies therefore did not meet our strict inclusion criteria in that they do not perform a whole-brain analysis when comparing the TS group to controls. However, we acknowledge the contribution of these studies to the published literature on TS. We therefore conducted an exploratory ALE meta-analysis that incorporated these additional four studies, including contrasts that examined the group difference within task ROIs. These additional four studies are detailed in **Supplementary Table 2** and references listed in **Supplementary Table 3**. All ALE procedures were the same as for the primary group difference analysis (above). The results did not substantially change the clusters in the resulting ALE map (**Supplementary Table 5**) and therefore will not be further discussed.

2.4. ALE Meta-analysis: tic severity

We next examined the relationship between activations and tic severity in TS. We conducted a second ALE meta-analysis on neuroimaging studies that reported activation coordinates for correlations with tic severity in TS participants. Suitable studies were identified using the aforementioned inclusion criteria (see section 2.1). We discarded all criteria regarding the control group, as they bare no relevance to symptom severity analyses. As a result, 7 fMRI publications (**Table 2**) met inclusion criteria for this meta-analysis, one of which (Debes et al., 2011) found no correlation with symptom severity, and was thus used with no coordinates. Together, these articles provided information about 8 experiments with 23 foci and 378 participants. All studies measured tic severity with the Yale Global Tic Severity Scale (YGTSS). The reference list of the publications included in this tic severity meta-analysis can be found in **Supplementary Table 4**. ALE procedures were the same as for the group difference analysis (section 2.3).

First Author	Year	fMRI/ PET	No. TS	No. Con	Age TS (range)	OCD/ADHD	Meds	Task Nature	Task: Contrast
Buse (b)	2016	fMRI	17	23	Adolescents (11-17)	-	5	Auditory	Harmonic expectancy violation paradigm: harmonic vs disharmonic
Debes	2011	fMRI	39	37	Adolescents (M=13.9, SD=2.1)	12/7	-	Cognitive, Motor	Stroop: correct congruent vs correct incongruent Go-No-Go: correct no-go vs correct go Finger tapping: finger tapping vs rest
Deckersbach	2014	fMRI	8	8	Adults (21-37)	1/0	5	Cognitive	Visuospatial priming: negative vs neutral prime, positive vs neutral prime
Ganos	2014	fMRI	14	15	Adults (18-46)	-	3	Cognitive	Visual stop-signal task: stop-success > go
Marsh	2007	fMRI	66	70	Children (8-17) Adults (17-52)	10/6	36	Cognitive	Stroop task: correlation of brain activation with the "Stroop interference measure"
Zapparoli	2016	fMRI	24	24	Adults (19-54)	16/0	17	Motor	Execute movement: right hand > rest,

									left hand > rest Imagine movement: right hand > rest, left hand > rest
Zebardast	2013	fMRI	17	16	Adults (21-59)	12/9	Many*	Somatosensory	PPI: prepulse > pulse alone

Table 2. Studies included in the meta-analysis examining correlations with tic severity in TS. No. TS/Con – number of TS and control participants, respectively. OCD/ADHD – number of TS participants with comorbid OCD or ADHD. Meds – number of TS participants on medication.

* Publication provides only percentages of TS patients who take certain medications, which, however, are not mutually exclusive. It is thus not possible to tell exactly how many patients used medication.

3. Results

3.1 ALE Meta-analysis: TS vs controls group difference

The meta-analysis examining differences between TS and control participants was based on 14 publications (13 fMRI, 1 H₂O-PET) with a total of 651 participants, reporting 25 experiments and 311 foci. Fourteen activation clusters were identified in the resulting ALE image (**Figure 2**). TS participants showed differences in activations in lateral prefrontal cortex, including the inferior, middle, and superior frontal gyri; anterior cingulate cortex; lateral premotor cortex (precentral gyrus); supplementary motor area (SMA); posterior superior temporal sulcus; the supramarginal gyrus; retrosplenial cortex; secondary somatosensory cortex (postcentral gyrus); and the lingual gyrus. There were no subcortical clusters identified. See **Table 3** for cluster peak coordinates, volumes, and ALE values.

3.2 ALE Meta-analysis: tic severity

The meta-analysis testing for correlations with tic severity was based on 7 publications (all fMRI) with a total of 378 participants, reporting 8 experiments and 23 foci. Four activation clusters were identified in the resulting ALE image (**Figure 3**). Tic severity correlated with activations in the SMA, lateral premotor cortex (precentral gyrus), and lateral prefrontal cortex (middle frontal gyrus) (**Table 4**).

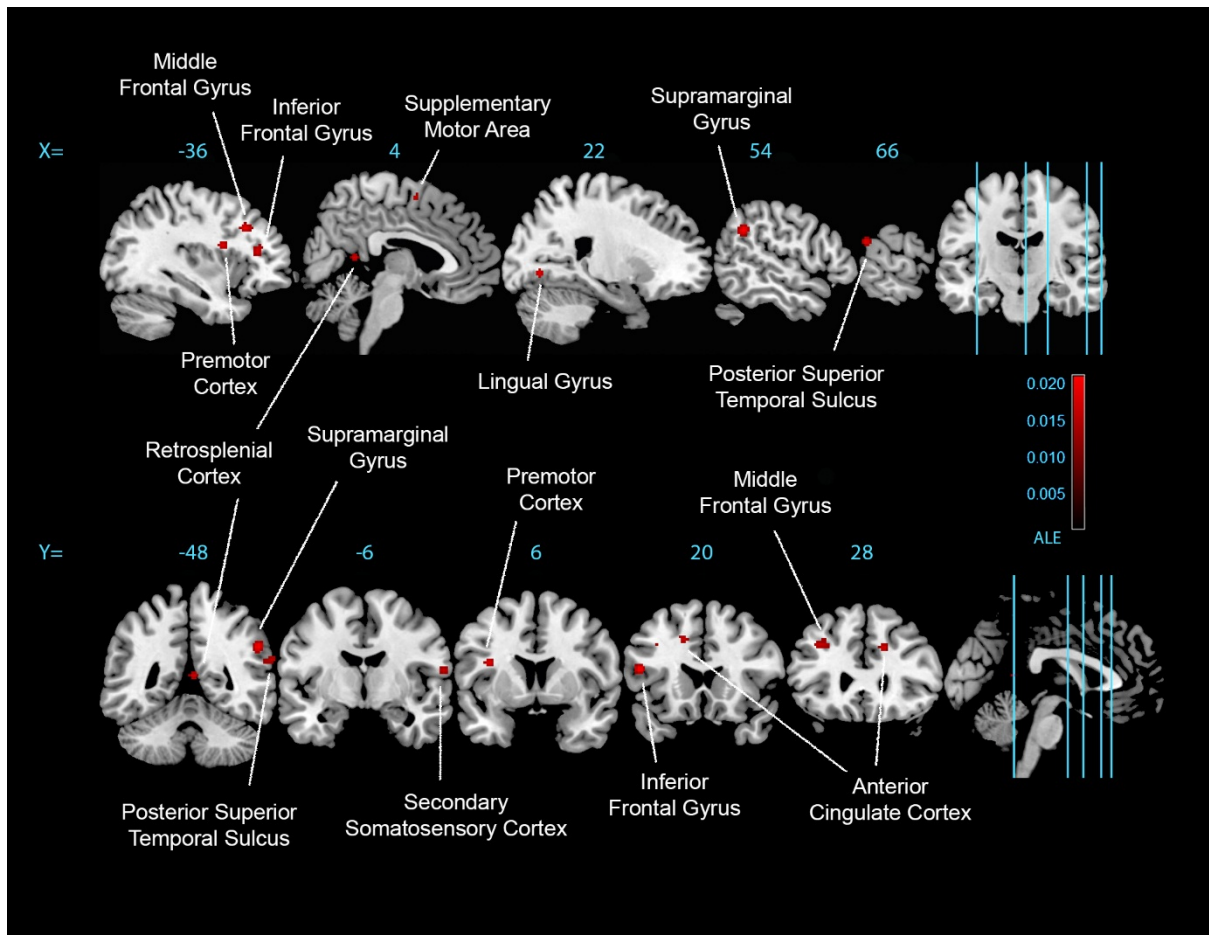


Figure 2. Results of the ALE meta-analysis showing differences in activation likelihood between Tourette Syndrome and control participants ($p < 0.001$, min. cluster size 100mm^3). Coordinates of sagittal (top row) and coronal (bottom row) slices given in MNI space. Colour bar represents the ALE statistic, which increases in significance from bottom (dark red) to top (bright red).

Cluster	Region	X	Y	Z	Cluster Volume (mm ³)	Extrema Value
1	L Inferior Frontal Gyrus	-38	34	16	680	0.0183
2	L Middle Frontal Gyrus	-36	24	34	560	0.0192
3	R Supramarginal Gyrus	54	-48	32	448	0.0209
4	L Inferior Frontal Gyrus	-50	20	14	384	0.0200
5	R Posterior Superior Temporal Sulcus	66	-46	22	296	0.0180
6	L Precentral Gyrus (Premotor Cortex)	-36	6	20	224	0.0183
7	R Anterior Cingulate Cortex	16	28	32	184	0.0166
8	R Lingual Gyrus (V4v)	22	-72	-4	160	0.0182
9	R Retrosplenial Cortex	4	-48	10	160	0.0166
10	R Postcentral Gyrus (Secondary Somatosensory Cortex S2)	62	-6	14	152	0.0167
11	L Anterior Cingulate Cortex	-14	20	38	152	0.0166
12	R Superior Frontal Sulcus	16	42	28	136	0.0154
13	L Superior Frontal Gyrus	-14	32	38	136	0.0161
14	R Supplementary Motor Area	4	0	60	104	0.0148

Table 3. GingerALE meta-analysis clusters and peak coordinates of differences in activation likelihood between Tourette Syndrome and control participants ($p < 0.001$ uncorrected, min. cluster size 100mm³). Anatomical localization was guided by the Anatomy toolbox for SPM12 and the Harvard-Oxford Cortical Structural Atlas in FSL. L – left hemisphere, R – right hemisphere. X,Y,Z – cluster peak MNI coordinates.

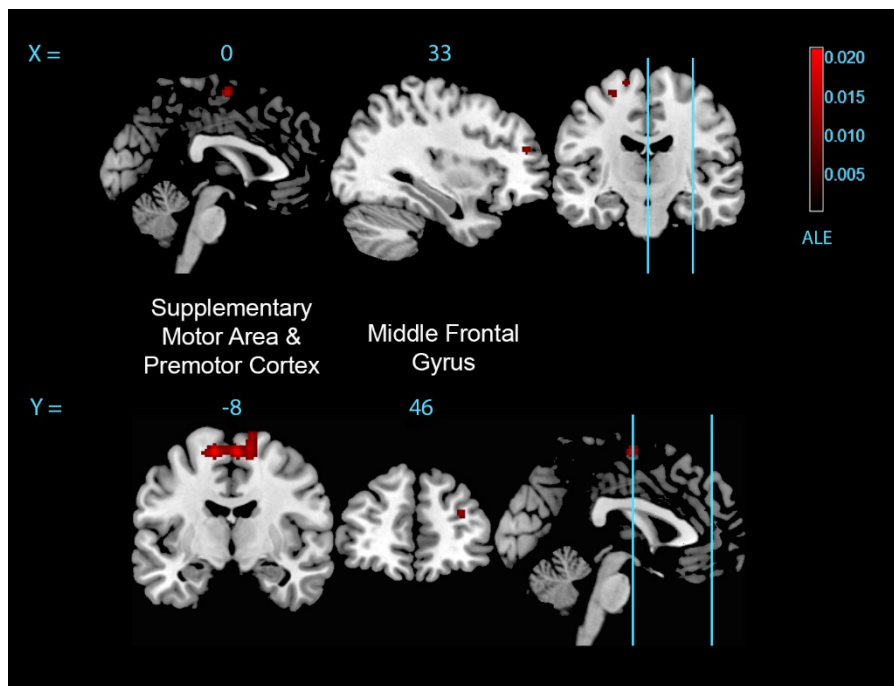


Figure 3. Results of the ALE meta-analysis showing activation likelihood associated with tic severity ($p < 0.001$, min. cluster size 100mm^3). Coordinates of sagittal (top row) and coronal (bottom row) slices given in MNI space. Colour bar represents the ALE statistic which increases in significance from bottom (dark red) to top (bright red).

Cluster	Region	X	Y	Z	Cluster Volume (mm ³)	Extrema Value
1	L Supplementary Motor Area	-12	-8	64	2832	0.0171
	R Supplementary Motor Area	4	-10	62		0.0164
	R Supplementary Motor Area	14	-6	66		0.0127
	R Supplementary Motor Area	14	-8	72		0.0108
	L Precentral Gyrus (Premotor Cortex)	-20	-12	58		0.0103
2	L Precentral Gyrus (Premotor Cortex)	-16	-18	70	144	0.0098
3	R Middle Frontal Gyrus	32	46	20	128	0.0103
4	L Precentral Gyrus (Premotor Cortex)	-26	-16	62	112	0.0098

Table 4. GingerALE meta-analysis clusters and peak coordinates of task activity correlations with tic severity ($p < 0.001$ uncorrected, min. cluster size 100mm³). Anatomical localisation was guided by the Anatomy toolbox for SPM12 and the Harvard-Oxford Cortical Structural Atlas in FSL. L – left hemisphere, R – right hemisphere. X, Y, Z – cluster peak MNI coordinates.

4. Discussion

We performed meta-analyses of task-based neuroimaging investigations of TS patients and controls, to obtain an overview of the anatomically widespread abnormalities of neural function reported across different studies. Furthermore, we tested for task activation patterns that specifically relate to core TS symptoms, by examining correlations with tic severity within TS patients. Group differences were identified in functional systems including prefrontal and motor preparation areas; sensory-perceptual (somatosensory and visual) areas; and parieto-temporal association cortices. Importantly, however, only prefrontal and motor preparation regions predicted tic severity, suggesting specificity of task-based neural reactivity within these areas to the core symptomatology of TS.

These results support a core dysfunction of CSTC motor loops in TS that specifically underpins the expression of tics (Alexander et al., 1986; Ganos et al., 2013; Worbe et al., 2013). Moreover, more generalized CSTC dysfunction may account for alterations across neuroanatomical systems predisposing individuals to the heterogeneity of intrinsic symptoms and the multifaceted nature of neuropsychiatric vulnerabilities within the TS spectrum (Ganos et al., 2013; Robertson, 2000).

4.1. Anatomically widespread alterations in neural function in TS

The neuroimaging studies of TS included in the meta-analyses were task-based studies that represented multiple experimental paradigms across cognitive domains. These included motor execution tasks, for example finger tapping (Roessner et al., 2013; Roessner et al., 2012; Werner et al., 2011; Zapparoli et al., 2016), motor inhibition tasks, for example the stop signal and Go/No-Go tasks (Debes et al., 2011; Ganos et al., 2014), executive function challenges, for example the Stroop task (Debes et al., 2011; Marsh et al., 2007), and probes of somatosensory gating, for example the prepulse (PPI) inhibition paradigm (Buse et al., 2016a; Zebardast et al., 2013), theory of mind tasks (Eddy et al., 2017; Eddy et al., 2016), and responses to emotional faces (Neuner et al., 2010). These neuroimaging investigations highlight the diversity of cognitive processes that are putatively altered in TS, which our first meta-analysis demonstrates are correspondingly reflected in differences in neural function, distributed anatomically across multiple neural systems.

Tics are fundamentally motor symptoms, and several motor execution and inhibition studies were included in the meta-analysis. We therefore anticipated that evidence for motor circuit

dysfunction would be identified: specifically, the meta-analysis highlighted cortical dysregulation within the motor preparation regions SMA and premotor cortex. We discuss the implications for understanding the dysfunction of these regions in reference to the tic severity ALE analysis in section 4.2.

The analysis of group differences also highlighted prefrontal clusters, encompassing all three frontal gyri. A high proportion of the included studies tested patients with comorbid ADHD and/or OCD, in which prefrontal dysfunction and associated executive deficits are likely core elements (Del Casale et al., 2016; Morein-Zamir et al., 2014; Vaghi et al., 2017). Thus, these prefrontal clusters may in part reflect the presence of, or predisposition to, these comorbid conditions in TS individuals.

Somatosensory features are important elements to the general experience of TS. Premonitory sensations frequently precede tics (Munchau et al., 2011; Thomalla et al., 2009). These are often described as feelings of 'itch' or 'pressure', and typically show a somato-homuncular coupling to the bodily location at which the tic subsequently emerges (Leckman et al., 1993). Our meta-analysis confirmed differences in the functional reactivity of somatosensory cortex (postcentral gyrus) in TS compared to controls, indicating how somatomotor control through cortico-cortical interaction might underpin the experiential expression of TS.

However, it is notable that the insula was not identified. Although the task-based studies included in our analysis did not explicitly test the neurobiological mechanisms of premonitory phenomena, the insula has been proposed as a core site of sensory symptom generation (Cavanna et al., 2017; Jackson et al., 2011; Worbe et al., 2015), and structural neuroimaging has confirmed severity of premonitory phenomena is associated with both somatosensory and insular cortices (Draganski et al., 2010; Draper et al., 2016). It is possible that while the insula is indeed a likely generator of sensory symptoms, it was not detected in our meta-analyses because task-based studies of TS to date have not typically employed paradigms testing bodily processing that are likely to activate the insula, such as interoceptive tasks (Critchley et al., 2004). Regardless of task nature, however, it would be useful if future task-based fMRI studies reported sensory symptom severity associations, as many studies in the existing literature do for tic severity, so that future meta-analyses can confirm if functional reactivity of the insula, alongside somatosensory cortex, are associated with this dimension of TS symptom expression. Of note, one resting-state fMRI study has already

indicated that strength of insula interactions with SMA is associated with premonitory phenomena severity (Tinaz et al., 2015).

Sensorimotor coupling and the priming of motor responses by sensation extends beyond proprioception and touch. Although the processing and representation of visual information has rarely been studied in TS, several visual processes appear to operate differently. Visual field (Enoch et al., 1991) and colour vision (Melun et al., 2001) deficits are both described in TS. Interestingly, the group difference analysis identified a cluster within lingual gyrus in the region of the colour perception area, V4. In addition, there are indications that perception of complex visual stimuli, namely facial expressions, is altered in TS. Participants with TS may show greater amygdala activation to emotional faces (Neuner et al., 2010), a possible driver for echopraxic facial tics, which more generally, highlights the influence of salient environmental stimuli on the sensitivity of people with TS to potential stressors (Conelea and Woods, 2008), including social emotional cues. Furthermore, a tendency for people with TS to engage in mental state reasoning, even when not explicitly required, may also promote greater neural reactivity in response to social and emotional cues (Eddy et al., 2017). While our meta-analysis cannot explicitly test for such mechanisms, group differences were observed across temporo-parietal areas implicated in own bodily self-consciousness, perception of others, and perspective taking; these included the posterior superior temporal sulcus, the supramarginal gyrus, and retrosplenial cortex (Beauchamp, 2015; Blanke, 2012; Eddy et al., 2016; Sulpizio et al., 2016).

Our first analysis demonstrated the presence of differences in cortical reactivity in TS, distributed across anatomically widespread neural systems. These differences may account for the wider set of cognitive affective and behavioral symptoms of the TS spectrum. Moreover it remains plausible that, in TS, a common process affecting cortical reactivity (e.g. compromised CSTC control) underpins these observations, with variable expression beyond the critical impact on tics. We therefore focused next on patterns of brain reactivity that might underpin the specific experience of tics in TS.

4.2 Tic severity is specifically associated with prefrontal and premotor activity

Regardless of comorbidities, developmental stage, or medication status, one symptom that all individuals with TS have in common is the expression of tics. We therefore performed an ALE meta-analysis to determine which regions show a specific relationship between task activity and tic severity.

A subset of premotor and prefrontal regions, encompassing the supplementary motor area, premotor cortex, and middle frontal gyrus were identified, indicating that the greater participants' tic severity, the greater the functional alterations in these regions. This corroborates the role of the supplementary motor area and premotor cortex in CSTC circuit dysfunction in TS (Ganos et al., 2013; Jackson et al., 2015; Worbe et al., 2015; Worbe et al., 2013). In addition, these data demonstrate the close relationship between prefrontal cortex function and tic expression, which may relate to inhibitory tic suppression strategies (Ganos, 2016), and influence the degree of plasticity in adaptive prefrontal regulation of motor responses (Jackson et al., 2015; Jung et al., 2013).

Interestingly, we did not observe any clusters within subcortical regions within this meta-analysis. Basal ganglia nuclei clearly play a role in tic expression (Bronfeld et al., 2011; McCairn et al., 2009) and are altered in structural morphology (Kataoka et al., 2010; Neuner et al., 2013). The thalamus also has a critical role within CSTC circuitry (Alexander et al., 1986), and is a therapeutic target for deep brain stimulation (Huys et al., 2016). In addition, there is evidence for TS-related structural and functional differences of the amygdala (Neuner et al., 2010; Neuner et al., 2013). That these subcortical structures were not identified in either the group difference or tic severity ALE analyses may reflect methodological insensitivity and the focus on task-based activation studies. Firstly, the particular subtractions used in these task-based studies may be less sensitive toward subcortical responses in whole-brain analyses. Secondly, although several studies employed paradigms relating to motor function, such as finger tapping, they did not examine symptom expression per se, other than broad correlations with tic severity. Thirdly, neurovascular coupling and the BOLD response differ in cortical and subcortical brain areas, with the result that neuroimaging studies may be more sensitive to group differences in cortical areas in general (Ances et al., 2008; Devonshire et al., 2012). Finally, the ALE methodology itself employs assumptions which may diminish the sensitivity of the analysis to detect results in subcortical regions (see 4.3 below).

4.3 ALE limitations

In establishing the pool of appropriate studies from the current TS neuroimaging literature for meta-analysis inclusion, a number of issues became apparent that have implications for the interpretation of our ALE results. We applied stringent selection criteria, requiring all studies to have conducted whole-brain analyses, report peak co-ordinates, and employed both a TS and a control group. Despite the burgeoning number of task-based neuroimaging investigations of TS,

unfortunately, many did not meet these basic criteria: most often, authors had not reported whole-brain investigations, and instead reported only group differences within pre-selected ROIs, negating the opportunity for the data to contribute to a meta-analysis, as this would a priori bias probability distributions produced by GingerALE towards the ROI foci.

This has two important implications. Firstly, our results do not encompass the entirety of available literature. Secondly, there appears to be a methodological tendency in a portion of task-based investigations of TS to examine specific regions-of-interest assumed to be of relevance for TS, or known to be important for the task. This contrasts with the use of whole-brain analyses that report which regions reach criterion threshold. The impact on meta-analytic investigations is that if non-significant whole-brain results are not reported, we are unable to enter that study to ALE analysis with zero co-ordinates. Thus, the group differences that we identify may be inflated. Therefore, even when ROIs are selected in clear relevance to the participant group and paradigms employed, we suggest it is helpful for future interpretation, and the pursuit of meta-analytic insights, that authors consistently report whole-brain statistical tests – even if non-significant – alongside ROI data.

The fact that (significant) whole-brain analyses are not more frequently reported may also reflect the subtle nature of differences in brain function in the neurodevelopmental disorder TS, when compared to neurodegenerative disorders (such as Parkinson's disease, Herz et al., 2014)). Indeed, beyond task-based fMRI investigations (Buse et al., 2016b; Debes et al., 2011; Hershey et al., 2004), neuroimaging studies of TS have not always revealed significant differences, including voxel-based morphology (VBM) studies of brain morphology (Jeppesen et al., 2014; Roessner et al., 2009; Wang et al., 2007); PET studies of striatal dopamine binding potential (Abi-Jaoude et al., 2015; Black et al., 2015), and magnetic resonance spectroscopy (MRS) studies of GABA concentration (Tinaz et al., 2014). This inconsistency in findings may be partly explained by heterogeneity of TS samples, including differences in sample size and variability in patient characteristics, in addition to differences in MRI hardware and methodology (Ganos et al., 2013).

The application of meta-analyses can provide powerful overviews of disparate literature. However, to draw robust conclusions, the extent of contributing literature matters. For task-based fMRI data analysed with GingerALE, in general, a sample size of approximately 20 studies is likely to yield sufficient power for moderate effects (Eickhoff et al., 2016). In our sample size of 14 studies, we identified multiple clusters of differences and effects in TS. However, these did not reach significance

at the most conservative thresholds for multiple comparisons correction. We therefore present our results with a degree of caution. Nevertheless, we identified an additional 7 studies that did not meet our stringent inclusion criterion for whole-brain analyses, and a further 6 studies that did not report activation coordinates. To test the impact of some of these otherwise eligible studies, we performed an additional exploratory analysis in which we included four task-ROI studies. Importantly, however, our results were not substantially different. Greater power and interpretive insight than was possible at present will benefit from future reporting of neuroimaging results within the TS literature at whole-brain thresholds, alongside more detailed reporting of clinical severity associations such as premonitory phenomena.

4.4. Future Directions

Future neuroimaging studies should carefully consider the complex presentation of TS, as the large proportion of individuals with comorbid disorders (Cavanna et al., 2009) may bias comparisons to unaffected participants (Ganos et al., 2014; Jackson et al., 2015). The direct comparison of 'pure' TS patients, TS participants with comorbidities, and control participants, will be of particular value, yet requires sufficient sample sizes. Medication status is another important aspect which should similarly be dealt with, by comparisons between medicated and medication-free patients, given that medication can modulate cognitive function and behavior (Worbe et al., 2011). Even in the case of smaller, mixed samples, the accurate reporting of the presence and severity of comorbidities will refine interpretation across the imaging literature.

An increased interest in resting-state fMRI studies of TS is apparent, as is evident in publications from 2014-2015 (Greene et al., 2015). However, our examination of the current fMRI literature on TS highlights the need for further task-related fMRI, reporting whole-brain results, to provide unique data on evoked neural reactivity that can complement and inform the interpretation of resting-state functional connectivity datasets. The constrained use of ROI analysis can be valuable for testing specific hypotheses regarding putative neural mechanisms, yet the approach can lead to an overrepresentation of selected brain regions within the literature, and underrepresentation of others (Sprooten et al., 2017). This circumvents the ideal application of meta-analytic approaches, since ROI studies introduce *a priori* increases in the likelihood of identified foci. Finally, network analysis methods, such as dynamic causal modeling (DCM) (Friston et al., 2013), permit greater insight into mechanistic pathways of dysfunction beyond increases or decreases in regional activity. These

approaches hold the potential for unveiling network integration changes, even if no activation differences are found within individual nodes of the network (Rae et al., 2016; Rowe, 2010). Thus, even if only subtle univariate results are observed, it is possible to reveal disorder-specific effects.

4.5 Conclusions

Using GingerALE meta-analysis, we found differences in neural activity in TS across multiple regions of neocortex, encompassing motor, somatosensory, and perceptual systems. However, only premotor and prefrontal areas were specific to the core expression of tics in TS. This accords with models of CSTC circuit dysfunction as fundamentally underpinning aspects of TS. The heterogeneity of TS, and methodological limitations within the existing task-based neuroimaging literature, invite future investigations to carefully delineate their sample populations and analysis reports.

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